CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 20-708/S-011

STATISTICAL REVIEW(S)

Statistical Review and Evaluation
Clinical Studies[1]

Date:

NDA #: 20-011/S021 and 20-708/S011

Applicant: TAP Pharmaceutical Products, Inc.

Name of Drug: Lupron Depot® 3.75mg

Indication: Management of endometriosis for 12 months

Documents Reviewed: Vol. 38.1-38.26, June 2001 Addendum, and A32.1 for NDA 20-011;
Vol. 26.1 for NDA 20-708 (revised label only)

Statistical Reviewer: Kate Meaker, M.S. (HFD-715)

Medical Input: Scott Monroe, M.D. (HFD-580)

Overview

Lupron Depot 3.75 mg currently is approved for the treatment of endometriosis for up to 6 months. The duration is limited because extended exposure may put patients at risk of reduced bone mineral density, among other side effects. This application requests that the treatment duration be extended to 12 months for a treatment regimen of Lupron Depot 3.75 mg in combination with norethindrone acetate 5 mg.

Two clinical studies were submitted for this application (see Table 1). Study M92-878 was a parallel-arm, double-blind study that allowed for comparisons of the 12-month Lupron Depot (LD-only) treatment regimen, not the approved duration, to the 12-month Lupron Depot plus norethindrone acetate (LD/N) desired treatment regimen. Study M97-777 was an open-label, single-arm study of the LD/N treatment regimen which provided additional safety data and only supportive efficacy information.

Lupron Depot is currently approved in the 3.75 mg 1-month dose (NDA 20-011) and in an 11.25 mg 3-month dose (NDA 20-708). The applicant submitted results from two clinical studies under application NDA 20-011/S021. These studies only included the 3.75 mg 1-month dose, not the 11.25 mg 3-month dose. The applicant concurrently submitted a label

[1] Keywords: clinical studies

revision request to NDA 20-708/S011 for the 11.25 mg 3-month dose. There is no clinical study data to assess for the label revision for the 3-month dose.

Table 1: Summary of Clinical Studies

Study Number (Dates Conducted)	Number of Centers (Locations)	Total Sample Size	Type of Control	Design	Duration of Treatment
M92-878 (11/93 – 12/97)	26 (all U.S.)	Lupron Depot Only (n=51) Lupron Depot + norethindrone acetate 5 mg/day (n=55)	Active	Phase IV Double-blind Randomized Parallel group	12 months
M97-777 (2/98 – 3/00)	24 (all U.S.)	Lupron Depot + norethindrone acetate 5 mg/day (n=136)	Historical: Lupron Depot Only group from M92-878	Open-label Single-arm	12 months

STUDY #M92-878

Background

This was a double-blind, randomized, multicenter, parallel-group, active-control study. The main objective was to determine the safety and efficacy of Lupron Depot 3.75 mg alone and in combination with estrogen and/or progestin add-back regimens for the treatment of endometriosis. The treatment duration was 52 weeks, with a 24-month post-treatment follow up period.

There were 4 treatment arms in this study, but only two of them are of interest for consideration here. Specifically, the goal of this application is to compare the Lupron Depot alone (LD-only) treatment regimen to the Lupron Depot plus norethindrone acetate 5 mg/day add-back (LD/N) treatment regimen. The other two treatment groups received Lupron Depot plus norethindrone acetate plus estrogen add-back (LD/N/CEE) at 0.625 or 1.25 mg/day treatment. The applicant did not pursue the LD/N/CEE treatment regimens. Placebos were given in place of the N and CEE add-back supplies to maintain the double-blind.

The primary efficacy endpoints are 5 signs and symptoms: dysmenorrhea, pelvic pain, deep dyspareunia, pelvic tenderness, and pelvic induration. Each of these was measured on a 4-point scale, with scoring of 1=none, 2=mild, 3=moderate, and 4=severe. These are the appropriate efficacy endpoints. The safety endpoint is the mean bone mineral density.

During the 52 week treatment period, patients received an injection of Lupron depot every 4 weeks at a clinic visit. The efficacy variables were measured at each of those visits. The bone mineral density was measured at Week 24 and Week 52 using DEXA methodology.

The patients were females, aged 18-40, with a diagnosis of endometriosis established by laparoscopy. Patients had to have moderate to severe pain in at least one of the following: pelvic pain not related to menstruation, deep dyspareunia, or dysmenorrhea. A total of 106 patients were randomized to the two treatment groups. The groups were similar with regard to demographic and disease status characteristics at baseline.

The disposition of the subjects in the two treatment groups was similar in terms of both the rate of, and reason for, drop-outs at any stage, as shown in Tables 2 and 3.

Table 2: Disposition of subjects by group (Study M92-878)

	LD-only		LD/N	
	n	%	n	%
Randomized	51	100%	55	100%
Intent-to-Treat (ITT)	50	98%	54	98%
Discontinued ≤ 24 Weeks	9	18%	13	24%
Discontinued ≤ 52 Weeks	19	37%	24	44%

Source: Vol. 38.5, Figure 10.1a and Statistical Table 14.1_3

Table 3: Reasons for Discontinuation (Study M92-878)

	LD-only (N=51)		LD/N (N=55)	
	n	%	n	%
Discontinued ≤ 24 Weeks	9	18%	13	24%
Adverse Event	7	14%	9	16%
Patient Request	0	0%	0	0%
Other	2	4%	4	7%
Discontinued 25-52 Weeks	10	20%	11	20%
Adverse Event	2	4%	2	4%
Patient Request	3	6%	5	9%
Other	5	10%	4	7%

Source: Vol. 38.5, Statistical Table 14.1_3

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Applicant's Analysis

The intent-to-treat (ITT) patient population was all enrolled patients, using all available data. The last observation carried forward method was used for the primary efficacy analyses. If a subject did not have any on-treatment measurements for a given variable, they were not included in the analysis for that variable. Patients who indicated "no menses" on the clinical evaluation of pain and who did not indicate any pain rating for dysmenorrhea were defined to have no pain during menses. If the evaluation of deep dyspareunia was missing for a patient due to no intercourse, the patient was not included in the analysis of deep dyspareunia for the corresponding timepoint.

The applicant presented the efficacy results for each of the 5 signs and symptoms as the mean change from baseline. P-values were reported for tests on within-group changes from baseline, and on tests between the two groups comparing the difference in mean change. Those comparisons are not applicable for an active-control study design intended to show similarity. Therefore the p-values are not included here. The applicant concluded that both the LD-only and LD/N treatment regimens improved the endometriosis signs and symptoms from baseline, and that there was no significant difference between the two groups.

Table 4: Applicant's Efficacy Results: (Study M92-878)

	LD-only		LD/N		Between Group Comparison**	
Primary Efficacy Variables (ITT):	n	Mean Change from Baseline	n	Mean Change from Baseline	Difference (LD-only – LD/N)	95% 2-sided CI on Diff.
Dysmenorrhea	50	-1.9	54	-1.9	0.0	(-0.2, 0.2)
Pelvic Pain	50	-0.9	54	-0.8	-0.1 †	(-0.3, 0.2)
Dyspareunia	25	-0.6	30	-0.8	+0.2 ‡	(-0.1, 0.6)
Pelvic Tenderness	50	-0.8	52	-0.8	0.0	(-0.2, 0.2)
Pelvic Induration	50	-0.4	52	-0.4	0.0	(-0.1, 0.1)

Source: Vol. 38.5, Tables 11.4a,b, c, d, and e

† A negative value favors the LD-only treatment group.
‡ A positive value favors the LD/N treatment group.
** No meaningful clinical difference was defined.

The safety endpoint of interest is bone mineral density (BMD). This was measured at baseline and again after 24 and 52 weeks of treatment. The results were reported in terms of the percent change from baseline. I consulted with a statistician who reviews bone mineral density results for HFD-510 and was told that percent change from baseline is the appropriate scale for assessing BMD. In this active-control study, the comparison should be a confidence interval of the between-group difference.

Bone mineral density (BMD) was included in this study as a safety variable, not as an efficacy measure. It was measured at baseline, Week 24 and Week 52 during the treatment period, and months 8, 12, 16, 20, and 24 of the follow-up period. The mean percent change from baseline is the appropriate way to report BMD results.

The analyses presented by the applicant in the study report for M92-878 (Vol. 38.5, Section 12.5.3) included any measurements for wide timeframes around each desired timepoint. The Medical Officer felt these wide timeframes made the results hard to interpret. In the ISS, the applicant produced results using shorter (2-month) timeframes, which the Medical Officer preferred. Therefore, the 2-month interval results from the ISS (Section 3.10.1) are shown here. The applicant used an ANCOVA model with treatment and baseline BMD in the analysis of the percent change in BMD.

At each time point, the loss of BMD in the LD-only treatment group was greater than in the LD/N treatment group. These results favor the LD/N treatment regimen. The applicant concluded that the LD/N treatment group showed substantially lower loss of bone mineral density.

Table 5: Applicant's Results: Bone Mineral Density (Study M92-878)

	LD-only		LD/N	
	n	Mean % Change from Baseline	n	Mean % Change from Baseline
Week 24	38	-3.3%	41	-0.2%
Week 52	23	-6.5%	25	-0.8%
Final (LOCF)	41	-5.3%	42	-0.9%

Source: Vol. 38.16, Table 3.10a

Reviewer's Analysis

The applicant had calculated the mean change on the 4-point ordinal scale for each of the 5 signs and symptoms items. The Medical Officer requested that the efficacy results be summarized in terms of the percent of subjects who improved on each item. I used the number who had each sign/symptom at baseline as the denominator and calculated the percent that improved on treatment for each group. The between-group difference, along with 2-sided 95% confidence intervals (CI) on the difference, is included for comparing the two groups. These results are shown in Table 6. Due to the relatively small sample sizes, the confidence intervals are quite wide.

The protocol did not plan to analyze the 5 signs and symptoms items as the percent who improved. No meaningful clinical difference is applicable here, so no formal statistical conclusion on the similarity of the two groups can be made.

Table 6: Reviewer's Results: Percent of Patients Who Improved (Study M92-878)

	LD-only			LD/N			Between Group Comparison**	
Primary Efficacy Variables (ITT):	N	# improved/ # with symptom at baseline	% Impr.	N	# improved/ # with symptom at baseline	% Impr.	Difference (LD-only – LD/N)	95% 2-sided CI on Diff.
Dysmenorrhea	50	48/50	96%	54	54/54	100%	-4% ‡	(-9%, 1%)
Pelvic Pain	50	33/50	66%	54	38/52	73%	-7% ‡	(-25%, 11%)
Dyspareunia	40	24/34	71%	42	25/35	71%	0%	(-22%, 21%)
Tenderness	50	35/47	75%	52	40/48	83%	-8% ‡	(-25%, 8%)
Pelvic Induration	50	22/25	88%	52	19/24	79%	+9% †	(-12%, 30%)

Source: SAS data sets

† A positive value favors the LD-only treatment group.
‡ A negative value favors the LD/N treatment group.
** No meaningful clinical difference was defined.

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For the safety analysis, the applicant used an ANCOVA model with terms for treatment and baseline BMD in the analysis of percent change in BMD. The Medical Officer preferred to see the mean percent change by treatment group. These results are presented in Table 7, along with 2-sided 95% confidence intervals on the mean percent change for each treatment group.

Formal between-group comparisons were not made for this endpoint because the LD-only treatment is not approved for the 12-month treatment duration due to this safety risk. Also, a meaningful clinical difference was not predefined, so the confidence intervals cannot be compared to a fixed criterion. Therefore these results are limited to describing the potential risk for loss of BMD for either of these treatment regimens.

Table 7: Reviewer's Results: Bone Mineral Density (Study M92-878)

	LD-only		LD/N	
	n	Mean % Change from Baseline (95% 2-sided CI)	n	Mean % Change from Baseline (95% 2-sided CI)
Week 24	38	-3.3% (-3.9%, -2.7%)	41	-0.2% (-0.9%, 0.4%)
Week 52	23	-6.4% (-7.5%, -5.3%)	25	-0.9% (-2.0%, 0.2%)
Final (LOCF)	41	-5.3% (-6.1%, -4.4%)	42	-0.9% (-1.7%, -0.2%)

Source: SAS datasets

Conclusions - Study M92-878

This is an active-control study, comparing a new LD/N combination 12-month treatment regimen to an approved drug (LD-only) given for an unapproved 12-month treatment duration. There are two basic limitations in making statistical conclusions from this study.

The efficacy variables are the five endometriosis signs and symptoms. For each variable, a 2-sided confidence interval on the between-group difference is desired to assess similarity. However, in this study a meaningful clinical difference was not predefined to decide if the confidence intervals supported efficacy. In a general sense, after discussions with the Medical Officer, I would conclude that the efficacy results are similar, but this is not based on a formal statistical test.

The safety results present a different limitation. The LD-only treatment is only approved for up to 6 months of treatment due to the potential risk for loss of bone mineral density, among other potential side effects. A between-group comparison which concluded that the LD/N treatment had less BMD loss than the LD-only treatment would still not appropriately answer the safety concern regarding whether the LD/N regimen sufficiently protects against BMD loss. The Medical Officer will need to make this clinical decision without a formal statistical conclusion.

STUDY #M97-777

Background

Study M97-777 was an open-label, single-arm, multicenter study. All patients received the Lupron Depot plus norethindrone acetate 5 mg/day add-back (LD/N) treatment regimen for 52 weeks of treatment, with a 1-year follow-up post-treatment period. The primary objective was to assess the safety endpoint of loss of bone mineral density (BMD). The five endometriosis signs and symptoms efficacy endpoints were measured as secondary variables.

A total of 136 patients were enrolled. All were women, aged 18 to 40, with a diagnosis of endometriosis established by laparoscopy. Patients had to have moderate to severe pain in at least one of the following: pelvic pain not related to menstruation, deep dyspareunia, or dysmenorrhea.

The disposition of the subjects in this study is shown in Tables 8 and 9. The observed discontinuation rates and reasons were within the expectations of the Medical Officer for a study of this length.

Table 8: Disposition of subjects by group (Study M97-777)

	LD/N	
	N	%
Randomized	136	100%
Intent-to-Treat (ITT)	136	100%
Discontinued $\leq$ 24 Weeks	33	24%
Discontinued $\leq$ 52 Weeks	54	40%

Source: Vol. 38.11, Figure 10.1d and Statistical Table 14.1_3.1

Table 9: Reasons for Discontinuation (Study M97-777)

	LD/N (N=136)	
	n	%
Discontinued $\leq$ 24 Weeks	33	24%
Adverse Event	11	8%
Patient Request	10	7%
Worsening Symptoms/Addl. Trmt. Needed	5	4%
Lost to follow-up/Other	7	5%
Discontinued 25-52 Weeks	21	15%
Adverse Event	7	5%
Patient Request	4	3%
Worsening Symptoms/Addl. Trmt. Needed	1	1%
Lost to follow-up/Other	9	7%

Source: Vol. 38.11, Statistical Table 14.1_3.1

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Applicant's Analysis

The efficacy results from this study are for descriptive purposes only. The efficacy measures were planned as secondary objectives in this study. Also, it is a single-arm, open-label study so no between-group comparisons can be made. The applicant included analyses comparing the results for the LD/N group in this study to the LD-only group from study M92-878, but we do not feel those comparisons are appropriate for regulatory conclusions.

The intent-to-treat population for the efficacy analyses was appropriately defined as all patients using all available data. This included all patients with at least one observation on a given endpoint. The LOCF approach was used for missing data.

Table 10: Applicant's Results: (Study M97-777)

	LD/N	
Efficacy Variables (ITT):	N	Mean Change from Baseline
Dysmenorrhea	134	-2.1
Pelvic Pain	134	-1.2
Dyspareunia	94	-1.0
Pelvic Tenderness	134	-1.4
Pelvic Induration	134	-0.9

Source: Vol. 38.11, Table 14.2.1_5.1

The applicant concluded that the LD/N treatment regimen "provided significant clinical benefit in reducing the severity of endometriosis symptoms." This conclusion is based on statistically significant within-subject mean change from baseline severity and on comparisons to the LD-only treatment group from study M92-878. However we consider these results to only be descriptive and to serve a supportive role. Comparisons to study M92-878 are not appropriate for formal statistical conclusions.

The primary goal of this study was to investigate the safety endpoint: bone mineral density (BMD). These results are shown in Table 11. The primary time point of interest is End of Treatment. This corresponds to Week 52, with the last observation carried forward approach applied for subjects with no data at Week 52. The protocol stated that if the lower bound of the 2-sided 95% CI did not go below –2.2% the results would support the conclusion that the LD/N treatment regimen provided protection against loss of BMD. The lower bound of the CI at Week 52 is –1.7%, which meets the prespecified criterion.

The applicant concluded that the LD/N regimen provided significant protection against BMD loss, based on the lower bound of the 95% CI of (-1.4%, -0.5%). This conclusion meets the prespecified criterion. The applicant also makes additional comparisons to the results for the LD-only group from study M92-878, which are not appropriate.

Table 11: Applicant's Results: Bone Mineral Density (Study M97-777)

	LD/N	
	n	Mean % Change from Baseline; 95% CI
Week 24	105	-0.3% (-0.7%, 0.1%)
Week 52	77	-1.1% (-1.7%, -0.5%)
Final (LOCF)	115	-1.0% (-1.4%, -0.5%)

Source: Vol. 38.16, Table 3.10b

* The meaningful clinical difference was defined as -2.2%.

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Reviewer's Analysis

The applicant had calculated the mean change on the 4-point ordinal scale for each of the 5 signs and symptoms items. The Medical Officer requested that the efficacy results be summarized in terms of the percent of subjects who improved on each item. The protocol did not plan to analyze the 5 signs and symptoms items as the percent who improved. These results serve descriptive purposes only.

The percent of patients who improved for each sign or symptom are similar to the results for the LD/N treatment group in study M92-878. Therefore these results support the efficacy in that study.

Table 12: Reviewer's Results: (Study M97-777)

	LD/N		
Efficacy Variables (ITT):	N	# improved / # with symptom at baseline	% Improved
Dysmenorrhea	134	128/133	99%
Pelvic Pain	134	100/133	75%
Dyspareunia	94	67/85	79%
Pelvic Tenderness	134	118/133	89%
Pelvic Induration	134	87/100	87%

Source: SAS data sets

The applicant's presentation of the BMD results for study M97-777 was appropriate, and no further reanalysis was needed. The results from the single arm LD/N treatment group from study M97-777 met the prespecified criterion for safety with respect to the percent loss of BMD. No other conclusions can be drawn for BMD from this study.

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Katherine Meaker
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Mike Welch
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Additional Analyses

Study M97-777 included a 12-month post-treatment follow-up period for evaluating the long-term loss of BMD safety endpoint. These results were submitted in an amendment in June 2001. This was not the primary timepoint of interest for this endpoint, but is of interest to the Medical Officer who requested that these results be presented in my review. These are for descriptive purposes only, with no appropriate comparisons. The applicant concluded that a recovery trend was observed during the follow-up period.

Table 13: Applicant's Results: Bone Mineral Density 1 Year Post-treatment (Study M97-777)

	LD/N	
Post-Treatment Follow-up Evaluation	N=91 With follow-up data	Mean % Change from Baseline *; 95% CI
Month 8	89	-0.6% (-1.2%, 0.0%)
Month 12	65	0.1% (-0.6%, 0.7%)
Final (LOCF)	91	0.0% (-0.6%, 0.5%)

Source: Addendum June 2001, Table 12.5b.

* No meaningful clinical difference was defined.

Conclusions - Study M97-777

The primary goal of this study was to assess the loss of bone mineral density safety endpoint. The predefined criterion was that the lower bound of a 95% 2-sided confidence interval on the percent change from baseline could not be less than –2.2%. The results for the LD/N treatment regimen group meet this criterion, with a confidence interval of (-1.4%, -0.5%). Therefore this study supports the conclusion that the LD/N treatment regimen protects against loss of BMD. Formal statistical comparisons of this study to the LD-only treatment regimen from M92-878 are not appropriate.

The five endometriosis signs and symptoms efficacy variables were measured as secondary variables in this study and provide only descriptive information. The results are similar to those for the LD/N treatment group from study M92-878. No statistical comparisons or conclusions can be made.

Summary

The goal of this application is to request approval of a combination treatment regimen of Lupron Depot 3.75 mg plus norethindrone acetate 5 mg/day add-back (LD/N) treatment regimen for a 12-month treatment duration. Lupron Depot 3.75 mg currently is approved for the treatment of endometriosis for up to 6 months. The duration is limited because extended exposure may put patients at risk of reduced bone mineral density, among other side effects. The two clinical studies provided in this application were intended to assess the safety and efficacy of the 12-month LD/N combination treatment regimen versus a 12-month LD-only treatment regimen.

Study M92-878 included both the LD/N and LD-only treatment arms which allowed for direct comparisons. The efficacy was assessed using the five endometriosis signs and symptoms. Confidence intervals on the between-group differences suggest that the results are similar. However, no formal statistical conclusions could be made because the clinically meaningful difference was not predefined and confidence intervals were wide. Descriptive statistics for the primary safety endpoint, percent loss in bone mineral density, showed that the LD/N treatment group had less BMD loss than the LD-only group. Because the 12-month LD-only treatment duration is not approved, no formal between-group statistical test was done. The clinical relevance of these descriptive results will have to be decided by the Medical officer.

Study M97-777 was an open-label, single-arm study with only the LD/N treatment regimen. It was primarily intended to provide additional safety data, with efficacy outcomes measured as secondary variables. The safety endpoint was the percent loss of bone mineral density, with a predefined decision rule that the lower bound of the 2-sided 95% confidence interval could not exceed –2.2%. The results showed a confidence interval of (-1.4%, -0.5%) which met the requirements to support safety for the LD/N treatment regimen. The results for the five efficacy endpoints are similar to those seen in the LD/N group in study M92-878, but no statistical conclusions can be made for these results.

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Mathematical Statistician

Concur: Dr. Nevius

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cc:
Archival NDA 20-011
HFD-580
HFD-580/JBest, SMonroe, DHixon, SAllen
HFD-715/ENevius, MWelch, KMeaker, CAnello